## REMARKS

This Amendment responds to the Office Action mailed January 26, 2009. With this amendment, Applicants amend claims 1 and 4, and cancel claims 2 and 3. Applicants note that the Office has deemed claims 5-13 as being directed to non-elected subject matter and therefore withdrawn these claims from consideration. No new matter has been added with the present amendment. Support for the amendment can be found throughout the specification and claims as filed, including, e.g., in previously presented claims 1-13, and at pages 2, 8, and 10 of the specification. Claims 1-4 are pending and under consideration with this amendment.

Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority based on Japanese Application No. 2003-207698.

Drawings

Applicants also thank the Examiner for acknowledging receipt of Applicants' drawings, filed November 21, 2006, and for indicating acceptance of the same.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging receipt of the Information Disclosure Statements filed on January 18, 2008 and September 15, 2008 and for returning electronically signed copies of the Forms PTO-1449 submitted therein.

Claim Rejections – 35 U.S.C. § 101

The Action rejects claims 1-4 under 35 U.S.C. 101 as allegedly directed to non-statutory subject matter. In response, Applicants have amended the claims as suggested by the Examiner. Applicants respectfully request withdrawal of the rejections in view of the amendments.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 1-4 as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter. In particular, the Action asserts that recitation of "judging inflammatory disease" in claim 1 and "detecting the C/T polymorphism at nucleotide 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO:1" in claim 3 renders the claims indefinite.

In response, Applicants have amended the claims as suggested by the Examiner. Applicants respectfully request withdrawal of the rejections in view of the amendments.

Claim Rejections – 35 U.S.C. § 112, First Paragraph – Written Description

The Action rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Action asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors possessed the claimed invention at the time the application was filed.

In response, Applicants have amended the claims as suggested by the Examiner. Applicants respectfully request withdrawal of the rejections in view of the amendments.

Claim Rejections – 35 U.S.C. § 112, First Paragraph – Enablement

The Action also rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Action asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

Applicants respectfully note that, without expressing agreement with or acquiescence to the rejection, claims 1 and 4 have been amended. Claims 1 and 4 have been amended to change "inflammatory disease" to "arteriosclerotic disease." Applicants note that claim 1 now recites "[a] method for determining an increased risk of arteriosclerotic diseases in humans, which comprises detecting in a biological sample obtained from a human subject, said sample comprising nucleic acids from the subject, the presence or absence of a C at position 3279 of SEQ ID NO:1; wherein the presence of a C at position 3279 of SEQ ID NO:1 is indicative of an increase risk of arteriosclerotic disease." These amendments find support in the specification at, for example, pages 2, 8, and 10. Applicants also note that claims 2 and 3 have been canceled, consistent with the amendment to claim 1.

Applicants respectfully submit that the specification does enable a person skilled in the art to make and use the invention. Arguments addressing the factors showing enablement follow.

*Nature of the invention and breadth of the claims*

Applicants respectfully submit that the class of invention is diagnostics and molecular biology as well as population genetics. Generally speaking, prediction is difficult in some aspects of these fields of study. The present invention as claimed, however, is limited to determining an increased risk of arteriosclerotic disease based upon detecting a polymorphism in a biological sample. In particular, the claims are drawn to "[a] method for determining an increased risk of arteriosclerotic diseases in humans, which comprises detecting in a biological sample obtained from a human subject, said sample comprising nucleic acids from the subject, the presence or absence of a C at position 3279 of SEQ ID NO:1, wherein the presence of a C at position 3279 of SEQ ID NO:1 is indicative of an increase risk of arteriosclerotic disease."

Applicants respectfully submit that the claims are fully supported by the disclosure and therefore, the specification and claims enable a person skilled in the art to make and use the invention.

*Teachings in the Specification and Working Examples*

Applicants submit that the working example and the specification fully enable the present invention by providing ample direction and a detailed explanation as to how to perform the invention. The working example, on page 20 of the specificaiton, states that "galectin-1 and galectin-2 were found to bind to LTA (lymphotoxin-α), and functional variations in these gene products were found to have led to functional variations in LTA, which could be associated with susceptibility to myocardial infarction. Accordingly, novel single nucleotide polymorphisms (SNPs) in these genes were identified and discovered, and the discovered SNPs were used to subject about 2300 patients and about 2300 controls to the case-control association study. As a

result, it was found that the quantity of minor homozygotes (TT allele) of the novel SNPs (3279 C>T) in intron 1 of the galectin-2 gene was significantly small in myocardial infarction patients ($X^2$=25.3, P=0.0000005; odds ratio=1.6) (Table 1) (where the nucleotide number depends on the variant designation) (See pages 20-21 of the specification). This indicates that SNPs at nucleotide 3279 in intron 1 of galectin-2 are factors that act protectively in myocardial infarction and that functional variations in galectin-2 may be associated with myocardial infarction."

In addition, Applicants note that when the "nucleotide in position 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO: 1 is C (3279C in intron 1 of galectin-2), for example, the expression level of galectin-2 can be determined to be low" (see specification pages 7-8). "On the other hand, when the nucleotide in position 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene as shown in SEQ ID NO: 1 is T (3279T in intron 1 of galectin-2), it can be determined that inflammatory disease has not been developed or is less likely to be developed" (see specification pages 7-8). Therefore, Applicants submit that from the aforementioned findings, it can be understood that the difference of expression level of the galectin-2 gene due to SNP at position 3279 in intron 1 of the galectin-2 gene, affects the behavior of LTA, and is a predictor of arteriosclerotic disease.

Applicants further submit that LTA was known at the time of the filing of the present application as a gene product that is sensitive to an inflammatory disease such as coronary artery disease (see The PROCARDIS Consortium, European Journal of Human Genetics (2004) 12, p. 773), as well as myocardial infarction, both of which are types of arteriosclerotic disease. In addition, LTA is one of the cytokines produced during the earliest phase of the process of angiitis (or vasculitis). LTA activates the cytokines cascade by inducing other mediators such as

interleukin-1 and adhesion molecules. Inflammatory mediators such as cytokines are known to be involved in atheroma formation and atheroma lesions, so as to induce lumina thrombosis. Applicants submit that it can be concluded that arteriosclerotic diseases can be determined by examining the C/T polymorphism at nucleotide 3279 in the nucleotide sequence of intron 1 of the galectin-2 gene.

In view of the foregoing, Applicants submit that the specification includes a working example and a strong and very detailed description of the basis for the invention which, together, clearly support the presently claimed invention and enable a person skilled in the art to make and use the invention.

*State of the Art, level of skill in the art, and level of predictability*

Applicants submit that in the field of study of diagnostics and molecular biology used along with population genetics to determine disease association analysis, the state of the art is high. Despite this high state of the art, the present invention is predictable and enables one skilled in the art to make and use the invention. Applicants submit that in order for association analyses to be accurate and predictable, generally, there should be a hierarchization of the samples (sampling bias). Furthermore, Applicants note that it is ideal when comparing studies to evaluate comparable groups of uniform populations.

The Action asserts that unpredictability is shown by prior art and post-filing art, and the claims of the present invention generically encompass any mutation in the galectin-2 gene of any subject organism and that the claims of the present invention also encompass diagnostic methods in any subject organism (Office Action page 11, paragraphs 4-5).

Applicants note that the claims are no longer drawn to "one gene polymorphism in the galectin-2 gene of any subject organism," but rather, to "[a] method for determining an increased risk of arteriosclerotic diseases in humans, which comprises detecting in a biological sample obtained from a human subject, said sample comprising nucleic acids from the subject, the presence or absence of a C at position 3279 of SEQ ID NO:1; wherein the presence of a C at position 3279 of SEQ ID NO:1 is indicative of an increase risk of arteriosclerotic disease."

Applicants note that the Action relies on Hacker et al. (Gut, May 1997, Vol. 40, p. 623) to show unpredictability in associating any sequence content with a particular phenotype. In response, Applicants note that Hacker et al. was a study dealing with Crohn's disease and ulcerative colitis, and does not relate to "arteriosclerotic disease." Further, Hacker et al. studied the association between the HLR-DR2 allele and Crohn's disease. Applicants submit therefore that the conclusions or findings stated in Hacker et al. are not applicable to the present invention.

Applicants also note that the Action relies on Juppner (Bone, 1995, Vol. 17, p. 39S) to show unpredictability interspecies. In response, Applicants note that Juppner teaches that "despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct function characteristics," and does not teach gene association, and further, does not discuss the galectin-2 gene or arteriosclerotic disease. Applicants further submit that in light of the claims and Juppner's lack of relevant teachings, Juppner should not be applied to the present invention.

Applicants respectfully submit that generally, in association analysis, the hierarchization of samples (sampling bias) is important. In this regard, it is important to note that European and American people are not uniform populations. Therefore, association analysis should be

performed with hierarchization tests. With respect to Hacker et al., Lucentini (Scientist, Dec. 20, 2004, p. 20), and Hegele (Arterioscler. Throm. Vasc. Biol., 2002, Vol. 22, p. 1058), European and American people were studied, and the sample sizes of the groups studied were small. Therefore, the association data in these references do not provide sufficient guidance in determining the predictability, or a lack thereof, in associating a sequence with a phenotype. In this particular case, they do not provide sufficient guidance in determining the predictability in the association between the LTA gene and arteriosclerotic disease.

Applicants further note that the Action relies on the post-filing references Mangino et al. (Atherosclerosis, 2007, Vol. 194, p. 112) and Sedlacek et al. (J. Mol. Med. 2007, Vol. 85, p.997) to show the lack of association of same SNP as the present invention, rs7291467, in galectin-2 gene and myocardial infarction (Office Action page 13). In response, Applicants note that the subjects in Mangino et al. and Sedlacek et al. are German and the aforementioned sampling bias and the requirement for hierarchization tests exists, but were not performed. Furthermore, the genotype frequency is different between Japanese and German people, and neither study comprised populations as large as that disclosed in the instant specification. For this reason as well, these references should be discounted.

Applicants further note that Mangino et al. and Sedlacek et al. both concede weaknesses in their own studies. Sedlacek et al. state that their study may also have "several limitations" (see Sedlacek et al. at page 1003, left column) and Mangino et al. note that "differences will need to be resolved by studies of large dataset from other populations" (see Mangino et al. at page 115, left column). These statements further support Applicants' position that these references should be discounted.

Applicants also note that the Action relies on Kimura et al. (Tissue Antigens, Vol. 69, p. 265) to show the lack of association of same SNP as the present invention, rs7291467, in galectin-2 gene and myocardial infarction in the Japanese and Korean population (Office Action page 13). In response, Applicants note that Kimura et al. concedes weaknesses in their study as well. For example, Kimura et al. note on page 269, right column, that

> "[w]e acknowledge that these finding require additional studies, and there is an apparent study limitation here that we did not strictly match the background of risk factor for MI in the patients and controls. It also should be noted that evaluation of coronary atherosclerosis (affected vessels) was not performed in the controls."

Applicants further submit that in Kimura et al., the numbers of patient samples for Japanese and Korean peoples are both very small. As described in Kimura, the small number of samples significantly reduces the detection ability of association analysis. Further, in Kimura, the LTA SNP also shows negative data. However, the association of the LTA SNP with disease is demonstrated by the analysis using another Japanese population and European family. As an example of an analysis using European peoples, Applicants respectfully refer the Office to "The PROCARDIS Consortium, European Journal of Human Genetics (2004) 12, 770-774" which is enclosed herewith. In this article, the association of LTA Thr26Asp with coronary artery disease is shown by using a linkage equilibrium test, which is not affected by hierarchization, without using case-control association analysis.

Kimura et al. describes how in the Japanese control sample of this study, especially Jcont 2 (Japanese control group 2), 536 cases are autopsy samples, and are not patients of myocardial infarction. However, the presence or absence of other arteriosclerotic diseases (for example, angina pectoris, which may be followed by myocardial infarctions) is not mentioned. Further, it

has been demonstrated statistically that the population used in the present example (the scale of which is about 3.5 times as compared to the Japanese population of Kimura) does not involve sampling bias (Ozaki et al, Nature Genetics, 2002, 2006). However, in Kimura, such analysis has not been performed. Applicants submit that in view of the foregoing, the conclusions or findings stated in Kimura et al. should be discounted.

Applicants respectfully submit that state of the art, the level of skill in the art, and the predictability of the present invention, along with the specification and claims enable a person skilled in the art to make and/or use the invention.

*Quantity of experimentation required*

Applicants submit that no undue, burdensome experimentation is required for the current invention. Applicants submit that the present invention is straightforward and not complicated. The invention is directed to determining an increased risk of arteriosclerotic disease in humans by detecting the presence or absence of C at position 3279 of SEQ ID NO:1 in galectin-2. The invention focuses on the presence or absence of C at position 3279: the presence correlates with an increased risk of the disease and the absence correlates with inflammatory disease being less likely of being developed or not being developed at all. Applicants submit that this test is not complicated; rather, it is very straightforward and does not require undue experimentation.

The Office's position appears to be that there is no correlation between the polymorphism and the disease state. If the Office is correct, no amount of experimentation will change that fact.

Applicants respectfully submit that in view of the foregoing, that the specification provides an adequate amount of direction and guidance to perform this invention without undue experimentation.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

**CONCLUSION**

In view of the foregoing, the Examiner is respectfully requested to withdraw the rejections of record and allow all the pending claims.

Applicants invite the Examiner to contact the undersigned with any questions.

Respectfully Submitted,
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